Barishal Univ. J. Bio-Sci. **3**(1): 65-74, 2024 (June) ISSN 2411-247X

OPTIMIZATION OF CHEMOTHERAPY DRUG REGIMENS WITH GENETIC ALGORITHM AND DOSE OPTIMIZER

SAJAL DEBNATH, RAHAT HOSSAIN FAISAL*, MD. MINHAJ UL ISLAM,
SALMA AKTER KAKON, SILVIA SIFATH AND MD. SAMSUDDOHA

Department of Computer Science and Engineering, University of Barishal, Barishal-8200, Bangladesh.

Abstract

Precise dose scheduling strategies are necessary to enhance the efficacy of chemotherapy while avoiding unwanted effects. In addition, appropriate administration of medication ensures that therapeutic levels are maintained while allowing healthy cells to recuperate. Chemotherapy that is tailored to the cell cycle improves outcomes by selectively targeting cancer cells that are dividing, hence increasing effectiveness and minimizing harm to healthy cells. This paper presents a new method that integrates a genetic algorithm with a drug dose optimizer to create a system for scheduling chemotherapy drug doses that are specific to the cell cycle. The non-dominated sorting genetic algorithm-II (NSGA-II) addresses the challenge of optimizing multiple conflicting objectives, such as the identification and targeting of malignant cells, the preservation of normal cells, and the minimization of toxicity. The drug dosage optimizer is essential in evaluating the effects of optimized drug doses and making necessary adjustments to achieve the desired level of normal cell count. This system utilizes an extensive cell-cycle-specific mathematical model to measure important aspects of a patient's body during the chemotherapy process. Our proposed methodology has been extensively simulated and compared to current computational models. These assessments confirm that our technique is more efficacious compared to other methods described in the corresponding research.

Key words: Compartmental Model, Optimizer, Multi-objective optimization, NSGA-II, Cancer Chemotherapy.

Introduction

The significant number of deaths caused by cancer makes it a persistently serious worldwide health issue. According to the World Health Organization (WHO), it caused 9.7 million deaths in 2022, surpassing previous numbers of the overall world (WHO 2024). In Bangladesh, more than 150781 new cancer cases were recorded and 108137 deaths were estimated for 2020 (WHO 2024). This cancer can be recognized by a rapid growth and dissemination of aberrant cells, which can worsen the condition of the afflicted person and perhaps cause death if not identified and treated promptly (Shindi *et al.* 2020).

To treat this cancer, chemotherapy is a crucial part of cancer treatment because it has a unique ability to neutralize cancer by slowing its progression and causing the death of cancer cells (Dhieb *et al.* 2023). Oral or intravenous chemotherapy agents are widely employed as a primary therapy to address tumors, manage tumor size, inhibit growth, and specifically target cancer cells for elimination (Faisal *et al.* 2023). However, it is important to carefully administer chemotherapy doses to maintain a trade-off balance between its anti-cancer effects and the potential impact on normal cells (Faisal *et al.* 2023). Achieving a balance between optimizing treatment outcomes and minimizing harm to healthy cells is very important. Proper drug dose scheduling plays an essential role in achieving this balance.

*Corresponding author E-mail: <rhfaisal@bu.ac.bd>.

Additionally, the combination of compartmental models and cell cycle-specific chemotherapy has proven to be highly effective in the treatment of cancer (Alam *et al.* 2010, Alam *et al.* 2013). These approaches offer valuable insights into the distribution and elimination of drugs within thebody, facilitating the development of optimal dosing strategies (Leszczyński *et al.* 2020). By specifically targeting cancer cells during sensitive phases of the cell cycle, cell cycle-specific chemotherapy enhances treatment outcomes and reduces side effects (Alam *et al.* 2013, Panjwani *et al.* 2019). Moreover, the integration of genetic algorithms (GA) has greatly contributed to the field of cancer chemotherapy dose scheduling (Petrovski and McCall 2001). These algorithms offer a framework for simultaneously considering multiple objectives and constraints, enabling the identification of optimal treatment regimens. These regimens aim to achieve various goals, including maximizing tumor control, and minimizing toxicity to healthy cells, while also taking into account patient-specific constraints (Petrovski and McCall 2001).

Previous research has introduced different methods, such as parameterization and analytical gradient methods (Martin 1992), cell-cycle-specific mathematical models (Dua *et al.* 2008, Liang *et al.* 2006), genetic algorithms (GA) using adaptive elitist populations (Liang *et al.* 2006, Liang *et al.* 2008), distributed evolutionary control algorithms (Tan *et al.* 2002), and memetic algorithms (Liang *et al.* 2008). However, these open-loop schemes show incapability for regulating the drug dose in a precise manner. Further, feedback control-based genetic algorithm (GA) and genetic algorithm (MOGA) oriented I-PD control have also been introduced to improve the controlling system. These methods provide continuous tracking of numerous clinical output parameters which is not viable to implement these conditions. Recently, some alternative approaches have been introduced as mathematical model-based optimal control strategy (Das *et al.* 2021), modular fuzzy expert system-based method (Nayak *et al.* 2022), and nonlinear error function-based controller (Panjwani *et al.* 2021) for the management of anti-cancer drug delivery systems.

This research presents a novel approach for scheduling optimal cell cycle-specific chemotherapy doses, combining a genetic algorithm with a drug dose optimizer. A dose optimizer is essential in cancer chemotherapy dose scheduling as it enables the adjustment and optimization of treatment regimens based on individual patient responses, considering physiological indicators, tumor progression, and drug toxicity levels. In contrast to existing approaches that only depend upon suggested doses without considering after-effects, this method incorporates an optimizer on the suggested dose obtained from the genetic algorithm (GA). The dose is subsequently adjusted based on this optimizer, resulting in an enhanced dosing strategy that maximizes therapeutic outcomes while minimizing side effects.

The subsequent sections of the article are structured in the following manner. Section 2 presents the proposed methodology to find optimized chemotherapy schedule for cancer treatment, incorporating a cell cycle-specific mathematical model, Genetic algorithm (GA), and a drug dose optimizer. Section 3 presents the simulation and results. Finally, in Section 5, the paper concludes with a discussion and summary of the findings.

Materials and Methods

Optimizer-based genetic algorithm: Here, we outline our suggested approach for finding the most effective timetable for providing drug-dose chemotherapy to individuals with cancer. The method entails employing a two-compartment model that is specifically tailored for cell cycle-specific chemotherapy. In addition, we suggest using an Optimizer-based genetic algorithm (OGA) to calculate the most effective dosage of a medicine. The OGA is tasked with ascertaining the suitable dose quantity. By employing the given dosage and a mathematical model that is

specific to the cell cycle, it is possible to compute crucial factors such as the quantity of malignant cells, the quantity of normal cells, the amount of the drug, and its toxic effects. In order to provide a clear representation of the entire process, we illustrate the suggested structure of the most efficient scheduler in Fig. 1.

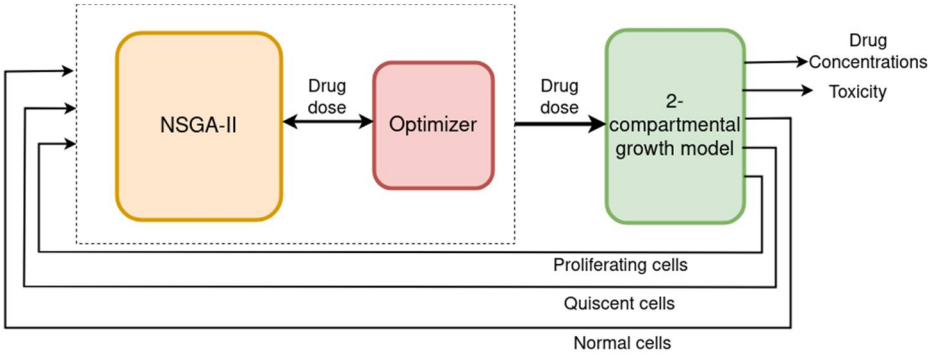


Fig. 1. Proposed architecture of the optimal scheduler.

Cell cycle-specific compartmental model: The cell cycle comprises the stages that both healthy and malignant cells go through, starting from their genesis and ending with their demise. These steps can be depicted using compartments that delineate discrete cell division stages or collections of stages organized into areas. The cell cycle generally entails five stages, as shown in Fig. 2. The proliferating compartment, which includes the pre-DNA synthesis (G1), synthesis (S), pre-mitotic (G2), and mitosis (M) phases, comprises of cells that are currently dividing and in a cycling state. On the other hand, the quiescent population (also known as the phase of relaxation or G0 phase) consists of cells that are in a phase of rest but have the ability to divide at a later stage in their life cycle (Dua *et al.* 2008).

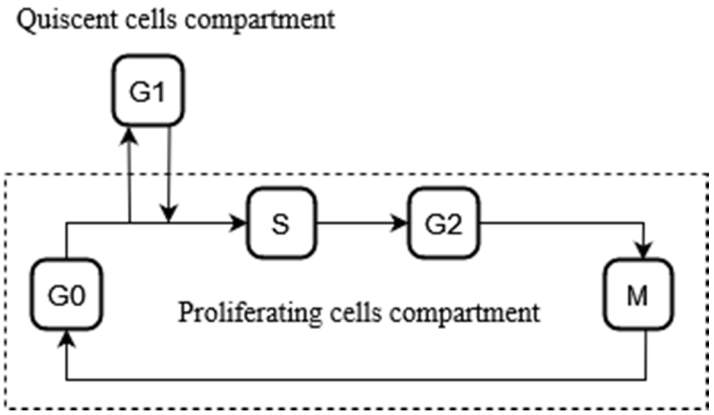


Fig. 2. Cell cycle-specific compartmental model.

In the present research, we utilized a two-compartmental model and implemented five differential equations (Panetta and Adam 1995, Dua *et al.* 2008) to analyze the behavior of both malignant and healthy cells in the patient's body. Based on clinical investigations, the initial

treatment stage consists of a cell compartment with 20% proliferating cells and 80% quiescent cells out of a total of 10^{12} cells (Panetta and Adam 1995). The study takes into account normal cells 10^9 because the cytotoxic chemicals used have the ability to kill equally malignant and healthy cells. The following formula (Panetta and Adam 1995, Dua *et al.* 2008) can be used to write the formulas provided as nonlinear equations:

$$\frac{dP}{dt} = (a-b-c)P(t) + dQ(t) - g(t)P(t) \quad (1)$$

$$\frac{dQ}{dt} = cP(t) - (d+e)Q(t) \quad (2)$$

$$\frac{dM}{dt} = \delta\left(1-\frac{M(t)}{K}\right)M(t) - g(t)M(t) \quad (3)$$

$$\frac{dD}{dt} = U(t) - \gamma D(t) \quad (4)$$

$$\frac{dT}{dt} = D(t) - \mu T(t) \quad (5)$$

$$\frac{dg}{dt} = \lambda D(t) \quad (6)$$

The equations given here demonstrate the different types of cells that exist in the body: proliferating cells, quiescent cells, and healthy cells, which are denoted as P(t), Q(t), and M(t) respectively. Equations (1), (2), and (3) describe how administrative drugs affect both cancerous and healthy cells. Additionally, Eq. (4) and (5) are used to estimate the fluctuations in drug levels in the patient's body, which helps determine the drug's adverse effects (Panetta and Adam 1995). Furthermore, Table 1 provides a detailed description of all the parameters linked to the medication Docetaxel.

Table 1. Parametric settings of cell cycle-specific chemotherapy model.

Parameter	Description	Value
a	Proliferating cell growth rate	0.5 cells per day
b	The degradation rate of Proliferating cells naturally	0.477 cells per day
c	The rate at which dividing cells transform into quiescent cells	0.218 cells per day
d	Quiescent cells to proliferating cells conversion rate	0.05 cells per day
e	Natural dying rate of quiescent cells	0.0173 cells per day
μ	Toxicity removal rate	0.4 per day
γ	Decay rate of docetaxel	0.25 per day
λ	Effect of docetaxel on cell death per unit of drug concentration per unit of time	0.0092 per day
δ	the rate of normal cell growth	0.1 per day
$D_i(t)$	Drug concentration	mg/ml
$U_i(t)$	Drug Dose	Mg/ml per day

Genetic Algorithm and Optimizer: NSGA-II is a multi-objective optimization approach that provides numerous excellent alternatives instead of only one optimum solution. It is an improvement upon classic genetic algorithms, with lower computing costs, preservation of

superior solutions, and enhanced constraint control. This approach enables designers to choose appropriate solutions by carefully considering and weighing different objectives. NSGA-II is a highly effective method for dealing with situations that have competing goals. It achieves this by using non-dominated sorting and crowding distance to provide a set of optimal alternatives. This approach allows for a wide range of solutions to be obtained. The design of this entails improving the adaptive fitness function of the population set in order to provide a Pareto front of the ideal solutions.

The impact of intravenously providing a medicine dose to a patient is substantial, particularly when the total number of healthy cells aligns closely with the minimum point of the healthy cell population, also referred to as the lower limit of normal cells. Administering a high dosage of the medicine is expected to cause a temporary decrease in the number of normal cells to a level below 10^8 for the following two to three days. According to the growth rate of normal cells shown in Table 1, the population of healthy cells will quickly return to 10^8 or greater within two or three days after the medicine is given. This scenario is suboptimal for an ideal chemotherapy scheduling system. Hence, there is a requirement for a drug dose optimizer that possesses the capability to compute or anticipate the subsequent impacts of drug doses.

The drug dose optimizer is specifically developed to compute the daily baseline cell count prior to providing the medication to the patient's body. The system employs a cell-cycle-specific mathematical model as the objective function and accepts each dose administered by the GA. In order to anticipate the consequences, the optimizer will compute the regular cell quantities for each day leading up to the seventh day before to providing the medicine dosage to the patient. The optimizer will generate the smallest measured healthy cell number from the estimated values for each day, up to the seventh day. If the lowest possible normal cell count falls close to or below the specified normal cell threshold (a user-adjustable parameter, such as 1.1*10^8, 1.4*10^8, 1.7*10^8, etc.), the optimizer will suggest reducing the drug dosage by a particular percentage, as outlined below:

- If N< 10^8, DRP = 20%
- If N>= 10^8 and N<=1.1*10^8, DRP =15%
- If N> 1.1*10^8 and N<= 1.2*10^8, DRP = 10%
- If N> 1.2*10^8 and N<= 1.4*10^8, DRP = 5%

In this context, N defines the amount of normal cells, while DRP denotes the percentage of reduction in dose. Additionally, the exact percentage of dose reduction will vary based on the user's preferences, and the consequences of the decrease will be comprehensively explained in the outcome assessment section.

The optimizer utilizes equations Eq. (3, 4, and 6) to calculate the concentration of the drug (docetaxel) within the patient's body, the efficacy of the medicine in killing cells, and to monitor the number of normal cells. These equations are the only foundation for calculating the concentration of dosage, the effect of cell destruction, and the total number of normal cells.

The design objectives, constraints, and parameters used for performance measurement in this proposed chemotherapy drug scheduling are as follows:

(i) Number of proliferating cells is 2 × 10^11 (Dua *et al.* 2008).

(ii) Number of quiescent cells is 8 × 10^11 (Dua *et al.* 2008).

(iii) Minimum number of normal cells is 1×10^8 (Dua *et al.* 2008, Alam *et al.* 2013).

$$M(t) > 10^8 \quad (7)$$

(iv) *Level of toxicity:* The maximum toxicity should not exceed 100 (Martin 1992, Dua *et al.* 2008, Alam *et al.* 2013).

(vi) *Drug doses:* The drug injected into the patient's body should be less than 50 (Panetta and Adam 1995, Dua *et al.* 2008, Alam *et al.* 2013).

i. *Number of treatment days:* The total number of days considered here is 86 days.

ii. *Total cancerous cell:* The first objective of the proposed scheduler is to maximize the effectiveness of the chemotherapy treatment by reducing the total cancerous cell number after 86th day.

$$Objective\ 1\colon Z1 = P(t) + Q(t) \quad (8)$$

iii. *Total normal cell:* The first objective of the proposed scheduler is to minimize the impact on normal cell populations.

$$Objective\ 2\colon Z2 = \int_0^{86} \left(10^9 - \frac{dM}{dt}\right) \quad (9)$$

Results and Discussion

We employed the MATLAB R2020a program to carry out development and simulation analyses for our NSGA-II and Optimizer-based chemotherapeutic drug dose controller. Additionally, the experiment was carried out for a total period of 86 days.

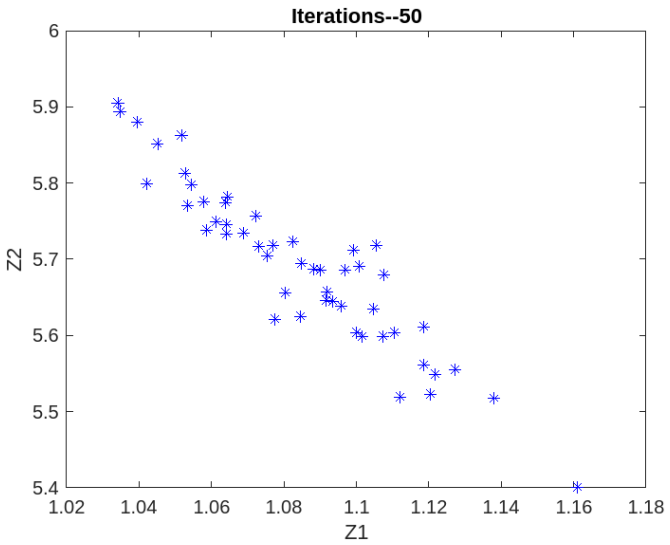
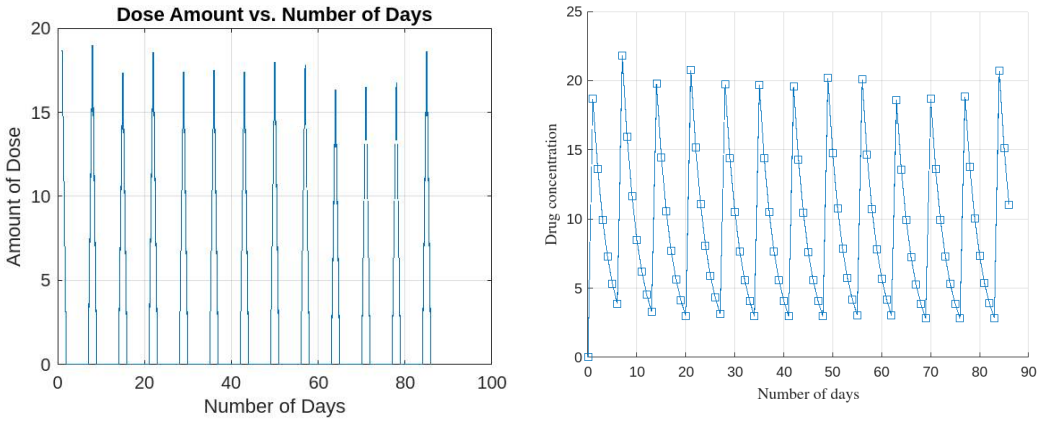


Fig. 3. Pareto font for optimal solutions.

The optimization technique entails employing 50 populations and conducting 50 iterations to collectively explore and seek for the ideal solution inside the search space. The population corresponds to the quantity of medicine dosage ranging from 15 to 20 units. The normal amount of

cells threshold is defined as 10^8, and the optimizer generates a drug dose reduction percentage. Both of these values can be modified according to user preferences and the patient's health status. Moreover, during the 86-day test period, the tumor stress characteristics are consistently observed. Once finished, the various optimum drug regimens are displayed in the search space, as shown in Fig. 3. This diagram presents a summary of the improved solutions obtained by the suggested system, showcasing the outcomes of a variety of drug doses with the given objectives.

Our research aims to develop an optimum structured schedule that efficiently minimizes the most severe tumor burden. In this case, a consistent interval of 7 days is used for administering various doses of chemotherapy. The duration between each treatment stays the same during the whole treatment period. During the optimization process, it has been noted that all the resulting optimized schedules guarantee that the dosage, denoted as u(t), remains under tolerable toxicity levels (100). In addition, these regimens also guarantee the maintenance of a level of normal cells that exceeds the minimum requirement throughout the whole treatment period.



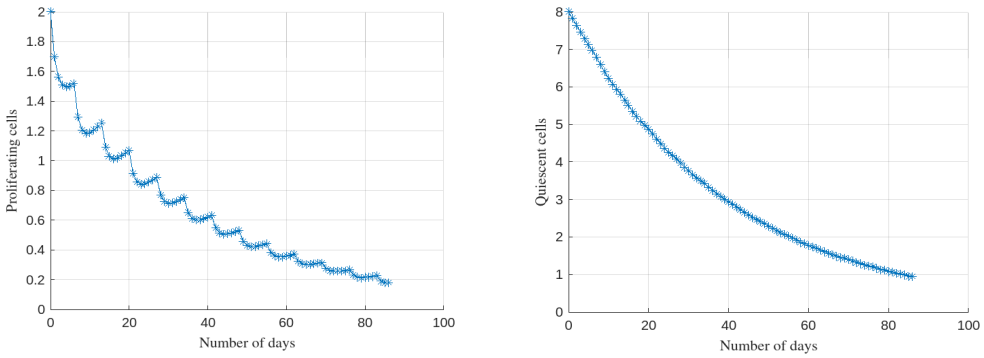
(a) Drug dose (b) Drug concentration

Fig. 4. Optimal chemotherapy dose schedule for 86 days and the drug concentration for applying the dose.

Figure 4(a) depicts the chosen treatment regimen, emphasizing the precise amounts and timing for each delivery. This graphic depiction offers a lucid comprehension of the best course of treatment. Furthermore, Fig. 4(b) illustrates the medication concentration in the individual's body following the administration of this optimized schedule. This data aids in evaluating the efficacy and dispersion of the medication within the patient's organism.

An essential goal of effective chemotherapy treatment is to decrease the number of actively dividing cells as well as the number of inactive cells, as both types have the ability to metastasize and spread cancer to vital organs. Our study estimates that the initial number of malignant cells before therapy starts is 10^12. Of this, 20% (2x10^11) are cells that are actively dividing, while the remaining 80% (8x10^11) are cells that are not actively dividing. This distribution corresponds with the results obtained in other investigations (Tan et al. 2002, Nayak et al. 2022). Furthermore, Fig. 5 visually illustrates the decrease in the quantity of malignant cells across the full duration of the treatment. The substantial reduction in the quantity of malignant cells across the span of 86 days is readily apparent. Figure 5(a) depicts the decrease in actively dividing cells, whereas Fig. 5(b) showcases the decrease in non-dividing cells as the treatment advances. At the conclusion of

the treatment, there are around 1.76x10^10 residual proliferating cells, indicating a decrease of 91.16%. Moreover, the estimated count of dormant cells that are still present is around 9.37x10^10, demonstrating a significant reduction of 88.28%. Together, these decreases in both types of cells contribute to an overall decrease of 88.86% in the amount of tumor present.



(a) (b)

Fig. 5. The impact of optimal chemotherapy dose schedule on (a) Proliferating cells and (b) Quiescent cells.

Figure 6(a) presents a comprehensive summary of the toxicity resulting from the medications provided during the entire treatment period. The toxicity levels related to the therapy regimen are maintained within the stipulated limits, assuring the safety and tolerability of the treatment. Additionally, the optimizer plays a crucial role in achieving tolerable toxicity values. By adjusting the suggested drug dose according to the patient's needs (Section 2.2.3), the optimizer ensures that the treatment remains within acceptable toxicity limits. This discovery highlights the efficacy of the optimal chemotherapeutic technique in efficiently managing and controlling drug-induced toxicity. Moreover, Fig. 6(b) demonstrates the effect of the harmful medicines on healthy cells. The graph clearly depicts the impact of the medications on the population of healthy cells over the treatment period. Although toxicity is present, the treatment technique used guarantees the survival of a significant number of healthy cells. After the treatment, the estimated number of normal cells that survived is 2.29 × 10^8 cells, indicating that the tailored chemotherapy successfully maintained the health and viability of the healthy cell populations.

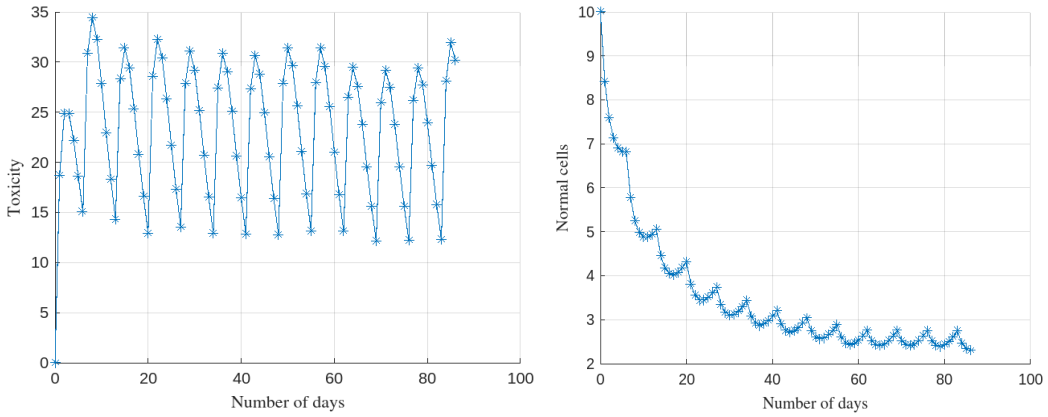
Table 2 displays a comprehensive evaluation of the effectiveness of the suggested methodology in comparison to other optimal control approaches employed in prior research attempts with comparable goals. The assessment is conducted using various crucial metrics, such as the decrease in the proportion of actively dividing cells and non-dividing cells, together with the count of healthy cells that remain after 86 days of treatment.

The results indicate that the proposed strategy surpasses the other strategies in effectively accomplishing the objective of cancer treatment. The proposed approach demonstrates the most significant decrease in both actively dividing cells and non-dividing cells, showing its efficacy in inhibiting the proliferation and metastasis of cancer cells. Moreover, the suggested methodology excels in maintaining a higher quantity of healthy cells in comparison to other alternative methods.

These data demonstrate the effectiveness of the suggested method in attaining the best possible results in cancer treatment. The proposed methodology demonstrates its usefulness and supremacy over other examined approaches through its superior performance, as seen by the reduction percentages and maintenance of normal cells.

Table 2. Comparing the effectiveness of the suggested approach to the current chemotherapy drag scheduling techniques.

	Proposed method	Panjwani *et al.* 2021	Pachauri *et al.* 2022	Dua *et al.* 2008	Pachauri *et al.* 2019	Algoul *et al.* 2010	Alam *et al.* 2013
% reduction in P cells	91.16	90.25	71.9	70	72.4	72.5	72.2
% reduction in Q cells	88.28	87	57	50	60.5	61	60.4
Number of Normal cells	2.299x10^8	1.8x10^8	1.03x10^8	1.05x10^8	1.009x10^8	1.03x10^8	1.0002x10^8



(a) (b)

Fig. 6. The impact of optimal chemotherapy dose schedule on (a) Toxicity and (b) Normal cells.

Conclusion

This research study introduces a new method for improving chemotherapy treatment by utilizing a Genetic Algorithm and a medication dose optimizer. Our work aimed to decrease the maximum tumor burden while minimizing damage and maintaining normal cell populations. By conducting thorough simulations and evaluations, we have effectively proven the usefulness and superiority of our proposed approach. The adjusted treatment regimens resulted in substantial decreases in both actively dividing and dormant cancer cells, hence reducing the likelihood of cancer metastasizing to vital organs. Furthermore, the suggested method effectively controlled toxicity levels, guaranteeing the patients' welfare during the entire therapy procedure. In addition, a substantial number of healthy cells were preserved, emphasizing the need to minimize the damage inflicted on healthy tissues during treatment. Our proposed strategy demonstrated greater performance compared to other optimal control approaches used in prior studies. The diminished percentages obtained and the number of normal cells surviving after 86 days exceeded those of other approaches, demonstrating the exceptional effectiveness of our methodology in accomplishing the aims of cancer treatment.

To improve the efficiency and usefulness of our suggested strategy, conducting further studies on clinical validation, multiple medicines, and incorporating elements of pharmacokinetics and pharmacodynamics is necessary. This can result in enhanced cancer treatment results and help to the advancement in chemotherapy efficiency.

References

Alam MS, Algoul S, Hossain MA and Majumder MAA 2010. Multi-objective particle swarm optimisation for phase specific cancer drug scheduling, In Computational Systems-Biology and Bioinformatics: First International Conference, CSBio 2010, Bangkok, Thailand, November 3-5, 2010. Proceedings. 180-192, Springer Berlin Heidelberg.

Alam MS, Hossain MA, Algoul S, Majumder MAA, Al-Mamun MA, Sexton G and Phillips R 2013. Multi-objective multi-drug scheduling schemes for cell cycle specific cancer treatment. Comput. Chem. Eng. **58**: 14-32.

Algoul S, Alam MS, Hossain MA and Majumder MAA 2010. Feedback control of chemotherapy drug scheduling for phase specific cancer treatment. *In:* IEEE fifth international conference on bio-inspired computing: theories and applications (BIC-TA). 1443-1450, IEEE

Das P, Das S, Das P, Rihan FA, Uzuntarla M and Ghosh D 2021. Optimal control strategy for cancer remission using combinatorial therapy: a mathematical model-based approach, *Chaos Solitons Fractals.* **145**: 110789.

Dua P, Dua V and Pistikopoulos EN, 2008, Optimal delivery of chemotherapeutic agents in cancer, Comput. Chem. Eng. **32**(1-2): 99-107.

Dhieb N, Abdulrashid I, Ghazzai H and Massoud Y 2023. Optimized drug regimen and chemotherapy scheduling for cancer treatment using swarm intelligence. Ann. Oper. Res. **320**(2): 757-770.

Faisal RH, Debnath S, Islam MMU, Sifath S, Kakon SA, Alam MS and Siddique N 2023. A modular fuzzy expert system for chemotherapy drug dose scheduling, Healthc. Anal. **3**:100139.

Leszczyński M, Ledzewicz U and Schättler H, 2020, Optimal control for a mathematical model for chemotherapy with pharmacometrics, Math. Model. Nat. Phenom. **15**: 69.

Liang Y, Leung KS and Mok TSK 2006. A novel evolutionary drug scheduling model in cancer chemotherapy. IEEE Trans. Inf. Technol. Biomed. **10**(2): 237-245.

Liang Y, Leung KS and Mok TSK 2008. Evolutionary drug scheduling models with different toxicity metabolism in cancer chemotherapy. Appl. Soft Comput. **8**(1): 140-149.

Martin RB, 1992, Optimal control drug scheduling of cancer chemotherapy, Automatica **28**(6): 1113-1123

Nayak J, Swapnarekha H, Naik B, Dhiman G and Vimal S 2022. Twenty five Years of Particle Swarm Optimization: Flourishing Voyage of Two Decades. Arch. Comput. Methods Eng. 1-63.

Pachauri N, Yadav D, Sharma TK, Verma OP and Ahn CW, 2022, Closed loop fractional order drug delivery control scheme for chemotherapy. Results Control Optim. **6**: 100097.

Pachauri N, Yadav J, Rani A and Singh V 2019. Modified fractional order IMC design based drug scheduling for cancer treatment, Comput. Biol. Med. **109**: 121-137.

Panetta JC and Adam J 1995. A mathematical model of cycle-specific chemotherapy, Math. Comput. Model. **22**(2): 67-82.

Panjwani B, Mohan V, Rani A and Singh V 2019. Optimal drug scheduling for cancer chemotherapy using two degrees of freedom fractional order PID scheme. J. Intell. Fuzzy Syst. 36(3): 2273-2284

Panjwani B, Singh V, Rani A and Mohan V 2021. Optimizing Drug Schedule for Cell-Cycle Specific Cancer Chemotherapy. *In:* Soft Computing: Theories and Applications: Proceedings of SoCTA 2020, Volume **2**: 71-81, Singapore: Springer Singapore

Petrovski A and McCall J 2001. Multi-objective optimisation of cancer chemotherapy using evolutionary algorithms, in Evolutionary Multi-Criterion Optimization: First International Conference, EMO 2001 Zurich, Switzerland, March 7-9, 2001 Proceedings **1**: 531-545

Shindi O, Kanesan J, Kendall G and Ramanathan A 2020. The combined effect of optimal control and swarm intelligence on optimization of cancer chemotherapy, Comput. Methods Programs Biomed. **189**: 105327.

Tan KC, Khor EF, Cai J, Heng CM and Lee TH 2002. Automating the drug scheduling of cancer chemotherapy via evolutionary computation, Artif. Intell. Med. **25**(2): 169-185

WHO, 2024, Cancer, https://www.who.int/news-room/fact-sheets/detail/cancer, accessed 25 March, 2024.